



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>A61K 31/135, A61P 11/00</b>	<b>A1</b>	(11) International Publication Number: <b>WO 00/51591</b> (43) International Publication Date: 8 September 2000 (08.09.00)
---	-----------	---

(21) International Application Number: PCT/EP00/01722 (22) International Filing Date: 1 March 2000 (01.03.00)  (30) Priority Data: 9904919.9 3 March 1999 (03.03.99) GB  (71) Applicant (for all designated States except AT US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, D-4058 Basel (CH).  (71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).  (72) Inventors; and (75) Inventors/Applicants (for US only): HASSAN, Ian, Francis [GB/GB]; 34 Kennedy Road, Horsham, West Sussex RH13 5DA (GB). CLARKE, Jeremy, Guy [GB/GB]; 8, Stirling Way, Horsham, West Sussex RH13 5RP (GB). DANAHAY, Henry, Luke [GB/GB]; 29 Furze Lane, Godalming, Surrey GU7 3NP (GB).  (74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
--	--

(54) Title: COMBINATIONS OF FORMOTEROL AND MOMETASONE FUROATE FOR ASTHMA

(57) Abstract

A medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or a solvate of the salt and (B) mometasone furoate, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## COMBINATIONS OF FORMOTEROL AND MOMETASONE FUROATE FOR ASTHMA

This invention relates to combinations of a beta-2 agonist and a steroid and their use for the treatment of inflammatory or obstructive airways diseases.

Formoterol, N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)-ethyl)phenyl]formamide, particularly in the form of its fumarate salt, is a bronchodilator used in the treatment of inflammatory or obstructive airways diseases. Mometasone furoate, (11 $\beta$ , 16 $\alpha$ )-9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methylpregna-1, 4-diene-3,20-dione, alternatively designated 9 $\alpha$ ,21-dichloro-16 $\alpha$ -methyl-1,4-pregnadiene-11 $\beta$ ,17 $\alpha$ -diol-3,20-dione 17-(2'-furoate), is a topical anti-inflammatory corticosteroid which is described in US4472393.

It has now surprisingly been found that a significant unexpected therapeutic benefit, particularly a synergistic therapeutic benefit, in the treatment of inflammatory or obstructive airways diseases can be obtained by combination therapy using formoterol, in free form or in the form of a salt or solvate thereof, and mometasone furoate. For instance, it is possible using this combination therapy to reduce the dosages of mometasone furoate or formoterol required for a given therapeutic effect considerably compared with those required using treatment with mometasone furoate or formoterol alone, thereby minimising possibly undesirable side effects. In particular, it has been found that these combinations, particularly as compositions containing formoterol and mometasone furoate, induce an anti-inflammatory activity which is significantly greater than that induced by formoterol or mometasone furoate alone and that the amount of mometasone furoate needed for a given anti-inflammatory effect may be significantly reduced when used in admixture with formoterol, thereby reducing the risk of undesirable side effects from the repeated exposure to the steroid involved in the treatment of inflammatory or obstructive airways diseases.

Furthermore, using the combination therapy of the invention, particularly using compositions containing formoterol and mometasone furoate, medicaments which have a rapid onset of action and a long duration of action may be prepared. Moreover, using such combination therapy, medicaments which result in a significant improvement in lung function may be prepared. In another aspect, using the combination therapy of the invention, medicaments which provide improved control of obstructive or inflammatory

airways diseases, or a reduction in exacerbations of such diseases, may be prepared. In a further aspect, using compositions of the invention, medicaments which can be used on demand in rescue treatment of obstructive or inflammatory airways diseases, or which reduce or eliminate the need for treatment with short-acting rescue medicaments such as salbutamol or terbutaline, may be prepared; thus medicaments based on compositions of the invention facilitate the treatment of an obstructive or inflammatory airways disease with a single medicament.

In one aspect, the present invention provides a medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or a solvate of said salt and (B) mometasone furoate, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

In another aspect, the present invention provides a method of treating an inflammatory or obstructive airways disease which comprises administering to a subject in need of such treatment effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined.

In a further aspect, the present invention provides a pharmaceutical composition comprising a mixture of effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined, optionally together with a pharmaceutically acceptable carrier.

The present invention also provides (A) and (B) as hereinbefore defined for use in combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

The invention further provides the use of (A) as hereinbefore defined or (B) as hereinbefore defined in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.

In a yet further aspect, the present invention provides a pharmaceutical composition for use in the treatment of an inflammatory or obstructive airways disease comprising (A) and (B) as hereinbefore defined.

The present invention still further provides the use of (A) and (B) as hereinbefore defined for the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

Pharmaceutically acceptable salts of formoterol include, for example, salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids such as fumaric, maleic, acetic, lactic, citric, tartaric, ascorbic, succinic, glutaric, gluconic, tricarballylic, oleic, benzoic, p-methoxybenzoic, salicylic, o- and p-hydroxybenzoic, p-chlorobenzoic, methanesulfonic, p-toluenesulfonic and 3-hydroxy-2-naphthalene carboxylic acids.

Component (A) may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, a mixture of enantiomers, a racemate or a mixture thereof. It may be in the form of a solvate, for example a hydrate, thereof, for example as described in US3994974 or US5684199, and may be present in a particular crystalline form, for example as described in WO95/05805. Preferably, component (A) is formoterol fumarate, especially in the form of the dihydrate.

Administration of the medicament or pharmaceutical composition as hereinbefore described, i.e. with (A) and (B) in admixture or separate, is preferably by inhalation, i.e. (A) and (B) or the mixture thereof are in inhalable form. The inhalable form of the medicament i.e. of (A) and/or (B) may be, for example, an atomizable composition such as an aerosol comprising the active ingredient, i.e. (A) and (B) separately or in admixture, in solution or dispersion in a propellant, or a nebulizable composition comprising a dispersion of the active ingredient in an aqueous, organic or aqueous/organic medium. For example, the inhalable form of the medicament may be an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant. In another example, the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium, or a combination of a dispersion of (A) in such a medium with a dispersion of (B) in such a medium.

An aerosol composition suitable for use as the inhalable form of the medicament may comprise the active ingredient in solution or dispersion in a propellant, which may be

chosen from any of the propellants known in the art. Suitable such propellants include hydrocarbons such as n-propane, n-butane or isobutane or mixtures of two or more such hydrocarbons, and halogen-substituted hydrocarbons, for example fluorine-substituted methanes, ethanes, propanes, butanes, cyclopropanes or cyclobutanes, particularly 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227), or mixtures of two or more such halogen-substituted hydrocarbons. Where the active ingredient is present in suspension in the propellant, i.e. where it is present in particulate form dispersed in the propellant, the aerosol composition may also contain a lubricant and a surfactant, which may be chosen from those lubricants and surfactants known in the art. Other suitable aerosol compositions include surfactant-free or substantially surfactant-free aerosol compositions. The aerosol composition may contain up to about 5% by weight, for example 0.002 to 5%, 0.01 to 3%, 0.015 to 2%, 0.1 to 2%, 0.5 to 2% or 0.5 to 1%, by weight of the active ingredient, based on the weight of the propellant. Where present, the lubricant and surfactant may be in an amount up to 5% and 0.5% respectively by weight of the aerosol composition. The aerosol composition may also contain a co-solvent such as ethanol in an amount up to 30% by weight of the composition, particularly for administration from a pressurised metered dose inhalation device.

In another embodiment of the invention, the inhalable form is a dry powder, i.e. (A) and/or (B) are present in a dry powder comprising finely divided (A) and/or (B) optionally together with a finely divided pharmaceutically acceptable carrier, which is preferably present and may be one or more materials known as pharmaceutically acceptable carriers, preferably chosen from materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, starches, dextran or mannitol. An especially preferred carrier is lactose. The dry powder may be in capsules of gelatin or plastic, or in blisters, for use in a dry powder inhalation device, preferably in dosage units of (A) and/or (B) together with the carrier in amounts to bring the total weight of powder per capsule to from 5 mg to 50 mg. Alternatively, the dry powder may be contained as a reservoir in a multi-dose dry powder inhalation device.

In the finely divided particulate form of the medicament, and in the aerosol composition where the active ingredient is present in particulate form, the active ingredient may have an average particle diameter of up to about 10  $\mu\text{m}$ , for example 0.1 to 5  $\mu\text{m}$ , preferably 1 to 5  $\mu\text{m}$ . The solid carrier, where present, generally has a maximum particle diameter up to

300  $\mu\text{m}$ , preferably up to 212  $\mu\text{m}$ , and conveniently has a mean particle diameter of 40 to 100  $\mu\text{m}$ , e.g. 50 to 75  $\mu\text{m}$ . The particle size of the active ingredient, and that of a solid carrier where present in dry powder compositions, can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, microprecipitation, spray-drying, lyophilisation or recrystallisation from supercritical media.

The inhalable medicament may be administered using an inhalation device suitable for the inhalable form, such devices being well known in the art. Accordingly, the invention also provides a pharmaceutical product comprising a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described in association with one or more inhalation devices. In a further aspect, the invention provides an inhalation device, or a pack of two or more inhalation devices, containing a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described.

Where the inhalable form of the active ingredient is an aerosol composition, the inhalation device may be an aerosol vial provided with a valve adapted to deliver a metered dose, such as 10 to 100  $\mu\text{l}$ , e.g. 25 to 50  $\mu\text{l}$ , of the composition, i.e. a device known as a metered dose inhaler. Suitable such aerosol vials and procedures for containing within them aerosol compositions under pressure are well known to those skilled in the art of inhalation therapy. For example, an aerosol composition may be administered from a coated can, for example as described in EP-A-0642992. Where the inhalable form of the active ingredient is a nebulizable aqueous, organic or aqueous/organic dispersion, the inhalation device may be a known nebulizer, for example a conventional pneumatic nebulizer such as an airjet nebulizer, or an ultrasonic nebulizer, which may contain, for example, from 1 to 50 ml, commonly 1 to 10 ml, of the dispersion; or a hand-held nebulizer, for example an electronically controlled device such as an AERx (ex Aradigm, US) or a mechanical device such as a RESPIMAT (Boehringer Ingelheim) nebulizer which allows much smaller nebulized volumes, e.g. 10 to 100  $\mu\text{l}$ , than conventional nebulizers. Where the inhalable form of the active ingredient is the finely divided particulate form, the inhalation device may be, for example, a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing a dry powder comprising a dosage unit of (A) and/or (B) or a multidose dry powder inhalation (MDPI) device adapted to deliver, for example, 3-25 mg of dry powder comprising a dosage unit of (A) and/or (B) per actuation. Suitable such dry powder inhalation devices are well known. For example, a suitable

device for delivery of dry powder in encapsulated form is that described in US3991761, while a suitable MDPI device is that described in WO97/20589.

The medicament of the invention is preferably a pharmaceutical composition comprising a mixture of (A) as hereinbefore defined and (B) as hereinbefore defined, preferably together with a pharmaceutically acceptable carrier as hereinbefore described.

The weight ratio of formoterol, or salt or solvate thereof, to mometasone furoate may be, in general, from 2:1 to 1:2000, for example from 1:1 to 1:1000, from 1:2 to 1:100, or from 1:5 to 1:50. More usually, this ratio is from 1:10 to 1:25, for example from 1:15 to 1:25. The two drugs may be administered separately in the same ratio. Specific examples of this ratio, to the nearest whole number, include 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18, 1:19, 1:20, 1:21, 1:22, 1:23, 1:24 and 1:25. The above weight ratios apply particularly where (A) is formoterol fumarate dihydrate. Thus, since the molecular weights of formoterol fumarate dihydrate and mometasone furoate are 840.9 and 521.4 respectively, the corresponding molar ratios of (A) to (B) may be, in general, from 1.24:1 to 1:3227, for example from 0.62:1 to 1:1613, from 1:3.2 to 1:161, or from 1:8.1 to 1:80.7; more usually from 1:16.1 to 1:40.3, for example from 1:24.2 to 1:40.3; specific examples of the molar ratio being 1:16.1, 1:17.8, 1:19.4, 1:21, 1:22.6, 1:24.2, 1:25.8, 1:27.4, 1:29, 1:30.7, 1:32.3, 1:33.9, 1:35.5, 1:37.1, 1:38.7 and 1:40.3.

A suitable daily dose of formoterol, or salt or solvate thereof, particularly as formoterol fumarate dihydrate, for inhalation may be from 1 to 72 µg, for example from 1 to 60 µg, generally from 3 to 50 µg, preferably from 6 to 48 µg, for instance from 6 to 24 µg. A suitable daily dose of mometasone furoate for inhalation may be from 50 to 2000 µg, for example from 100 to 2000 µg, from 100 to 1600 µg, from 100 to 1000 µg, or from 100 to 800 µg, preferably from 200 to 500 µg, for instance from 200 to 400 µg. The precise dose used will of course depend on the condition to be treated, the patient and the efficiency of the inhalation device.

A suitable unit dose of formoterol component (A), particularly as formoterol fumarate dihydrate, may be from 1 to 72 µg, for example from 1 to 60 µg, generally from 3 to 48 µg, preferably from 6 to 36 µg, especially from 12 to 24 µg. A suitable unit dose of mometasone furoate (B) may be from 25 µg to 2000 µg, for example from 50 µg to 1000 µg, preferably from 500 µg to 800 µg, more preferably from 100 µg to 500 µg, especially from 100 to 400 µg, e.g. from 200 to 400 µg. These unit doses may suitably be

administered once or twice daily in accordance with the suitable daily dose mentioned hereinbefore. For on demand usage, a dosage unit containing 6 $\mu$ g or 12  $\mu$ g of (A) and 50  $\mu$ g or 100 $\mu$ g of mometasone furoate (B) is preferred.

In one preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder in a capsule containing a unit dose of (A) and (B), for example for inhalation from a single capsule inhaler, the capsule suitably containing, where (A) is formoterol fumarate dihydrate, from 3  $\mu$ g to 36  $\mu$ g of (A), preferably from 6  $\mu$ g to 24  $\mu$ g of (A), especially from 12  $\mu$ g to 24  $\mu$ g of (A), and from 25  $\mu$ g to 800  $\mu$ g, e.g. 25 $\mu$ g to 500  $\mu$ g or 25  $\mu$ g to 400  $\mu$ g, of (B), preferably from 50  $\mu$ g to 400  $\mu$ g of (B), especially from 100 to 400  $\mu$ g of (B), together with a pharmaceutically acceptable carrier as hereinbefore described in an amount to bring the total weight of dry powder per capsule to between 5 mg and 50mg, for example 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg or 50mg, preferably 20 to 25 mg, especially 25 mg.

In another preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder for administration from a reservoir of a multi-dose dry powder inhaler adapted to deliver 3mg to 25mg of powder containing a unit dose of (A) and (B) per actuation, for example, where (A) is formoterol fumarate dihydrate, a powder comprising, by weight, 3 to 36 parts, preferably 6 to 24 parts, especially 12 to 24 parts of (A); 25 to 800 parts, e.g. 25 to 500 parts, preferably 50 to 400 parts, especially 100 to 400 parts of (B); and 2164 to 24972 parts, preferably 4164 to 14972 parts, especially 4164 to 9972 parts of a pharmaceutically acceptable carrier as hereinbefore described.

In accordance with the above, the invention also provides a pharmaceutical kit comprising (A) and (B) as hereinbefore defined in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts. Such a kit suitably further comprises one or more inhalation devices for administration of (A) and (B). For example, the kit may comprise one or more dry powder inhalation devices adapted to deliver dry powder from a capsule, together with capsules containing a dry powder comprising a dosage unit of (A) and capsules containing a dry powder comprising a dosage unit of (B). In another example, the kit may comprise a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (A) and a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (B). In a further example, the kit may comprise a metered dose inhaler containing an aerosol

comprising comprising (A) in a propellant and a metered dose inhaler containing an aerosol comprising (B) in a propellant.

Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis and emphysema, bronchiectasis and exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalcosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

The invention is illustrated by the following Examples, in which parts are by weight unless stated otherwise.

Example 1 - Aerosol Composition for Metered Dose Inhaler

Ingredient	% by weight
Formoterol fumarate dihydrate	0.012
Mometasone furoate	0.250
Ethanol (absolute)	2.500
HFA 227	60.768
HFA134a	36.470

Example 2 - Dry Powder

Ingredient	% by weight
Formoterol fumarate dihydrate	0.048
Mometasone furoate	1.000
Lactose monohydrate	98.952

Example 3

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO97/20589 is prepared by mixing 12 parts of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1-5 $\mu$ m in an air-jet mill, 250 parts of mometasone furoate which has been similarly ground to a mean particle diameter of 1-5 $\mu$ m and 4738 parts of lactose monohydrate having a particle diameter below 212 $\mu$ m.

Examples 4 - 92

Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
4	12	50	4938

5	12	100	4888
6	12	150	4838
7	12	200	4788
8	6	50	4944
9	6	100	4894
10	6	150	4844
11	6	200	4794
12	6	250	4744
13	18	50	4932
14	18	100	4882
15	18	150	4832
16	18	200	4782
17	18	250	4732
18	24	50	4926
19	24	100	4876
20	24	150	4826
21	24	200	4776
22	24	250	4726
23	30	50	4920
24	30	100	4870
25	30	150	4820
26	30	200	4770
27	30	250	4720
28	36	50	4914
29	36	100	4864
30	36	150	4814
31	36	200	4764
32	36	250	4714
33	6	50	9944
34	6	100	9894
35	6	150	9844
36	6	200	9794
37	6	250	9744
38	12	50	9938
39	12	100	9888

40	12	150	9838
41	12	200	9788
42	12	250	9738
43	18	50	9932
44	18	100	9882
45	18	150	9832
46	18	200	9782
47	18	250	9732
48	24	50	9926
49	24	100	9876
50	24	150	9826
51	24	200	9776
52	24	250	9726
53	30	50	9920
54	30	100	9870
55	30	150	9820
56	30	200	9770
57	30	250	9720
58	36	50	9914
59	36	100	9864
60	36	150	9814
61	36	200	9764
62	36	250	9714
63	6	50	14944
64	6	100	14894
65	6	150	14844
66	6	200	14794
67	6	250	14744
68	12	50	14938
69	12	100	14888
70	12	150	14838
71	12	200	14788
72	12	250	14738
73	18	50	14932
74	18	100	14882

75	18	150	14832
76	18	200	14782
77	18	250	14732
78	24	50	14926
79	24	100	14876
80	24	150	14826
81	24	200	14776
82	24	250	14726
83	30	50	14920
84	30	100	14870
85	30	150	14820
86	30	200	14770
87	30	250	14720
88	36	50	14914
89	36	100	14864
90	36	150	14814
91	36	200	14764
92	36	250	14714

### Example 93

Gelatin capsules suitable for use in a capsule inhaler such as that described in US3991761 are prepared, each capsule containing a dry powder obtained by mixing 12 $\mu$ g of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1 to 5 $\mu$ m in an air jet mill, 250 $\mu$ g of mometasone furoate which has been similarly ground to a mean particle diameter of 1 to 5 $\mu$ m and 24738 $\mu$ g of lactose monohydrate having a particle diameter below 212 $\mu$ m.

### Examples 94 - 152

Example 93 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
94	12	50	24938
95	12	100	24888
96	12	150	24838
97	12	200	24788
98	6	50	24944
99	6	100	24894
100	6	150	24844
101	6	200	24794
102	6	250	24744
103	18	50	24932
104	18	100	24882
105	18	150	24832
106	18	200	24782
107	18	250	24732
108	24	50	24926
109	24	100	24876
110	24	150	24826
111	24	200	24776
112	24	250	24726
113	30	50	24920
114	30	100	24870
115	30	150	24820
116	30	200	24770
117	30	250	24720
118	36	50	24914
119	36	100	24864
120	36	150	24814
121	36	200	24764
122	36	250	24714
123	6	50	19944
124	6	100	19894
125	6	150	19844

126	6	200	19794
127	6	250	19744
128	12	50	19938
129	12	100	19888
130	12	150	19838
131	12	200	19788
132	12	250	19738
133	18	50	19932
134	18	100	19882
135	18	150	19832
136	18	200	19782
137	18	250	19732
138	24	50	19926
139	24	100	19876
140	24	150	19826
141	24	200	19776
142	24	250	19726
143	30	50	19920
144	30	100	19870
145	30	150	19820
146	30	200	19770
147	30	250	19720
148	36	50	19914
149	36	100	19864
150	36	150	19814
151	36	200	19764
152	36	250	19714

Examples 153 - 176

Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
153	6	25	2969
154	6	50	2944
155	6	100	2894
156	6	150	2844
157	6	200	2794
158	6	250	2744
159	12	25	2963
160	12	50	2938
161	12	100	2888
162	12	150	2838
163	12	200	2788
164	12	250	2738
165	12	300	2638
166	12	350	2588
167	12	400	2538
168	24	25	2951
169	24	50	2926
170	24	100	2876
171	24	150	2826
172	24	200	2776
173	24	250	2726
174	24	300	2676
175	24	350	2626
176	24	400	2576

Examples 177-281

Example 93 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (µg)	Mometasone Furoate (µg)	Lactose Monohydrate (µg)
177	6	25	14969
178	6	50	14944
179	6	100	14894
180	6	150	14844
181	6	200	14794
182	6	250	14744
183	6	300	14694
184	6	350	14644
185	6	400	14594
186	12	25	14963
187	12	50	14938
188	12	100	14888
189	12	150	14838
190	12	200	14788
191	12	250	14738
192	12	300	14688
193	12	350	14638
194	12	400	14588
195	12	500	14488
196	24	25	14951
197	24	50	14926
198	24	100	14876
199	24	150	14826
200	24	200	13876
201	24	250	13826
202	24	300	13776
203	6	25	9969
204	6	50	9944
205	6	100	9894
206	6	150	9844
207	6	200	9794
208	6	250	9744

209	6	300	9694
210	12	25	9963
211	12	50	9938
212	12	100	9888
213	12	150	9838
214	12	200	9788
215	12	250	9738
216	12	300	9688
217	12	400	9588
218	12	500	9488
219	24	25	9951
220	24	50	9926
221	24	100	9876
222	24	150	9826
223	24	200	9776
224	24	250	9726
225	24	300	9676
226	24	400	9576
227	24	500	9476
228	6	25	4969
229	6	50	4944
230	6	100	4894
231	6	150	4844
232	6	200	4794
233	6	250	4744
234	6	300	4694
235	6	400	4594
236	6	500	4494
237	12	25	4963
238	12	50	4938
239	12	100	4888
240	12	200	4788
241	12	300	4688
242	12	400	4588
243	12	500	4488

244	12	25	24963
245	12	300	24688
246	12	400	24588
247	12	500	24488
248	12	25	19963
249	12	300	19688
250	12	400	19588
251	12	500	19488
252	6	600	4394
253	6	800	4194
254	12	600	4388
255	12	800	4188
256	24	600	4376
257	24	800	4176
258	6	600	9394
259	6	800	9194
260	12	600	9388
261	12	800	9188
262	24	600	9376
263	24	800	9176
264	6	600	14394
265	6	800	14194
266	12	600	14388
267	12	800	14188
268	24	600	14376
269	24	800	14176
270	6	600	19394
271	6	800	19194
272	12	600	19388
273	12	800	19188
274	24	600	19376
275	24	800	19176
276	6	600	24394
277	6	800	24194
278	12	600	24388

279	12	800	24188
280	24	600	24376
281	24	800	24176

Claims

1. A medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or a solvate of said salt and (B) mometasone furoate, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.
2. A medicament according to claim 1 which is a pharmaceutical composition comprising a mixture of effective amounts of (A) and (B), optionally together with a pharmaceutically acceptable carrier.
3. A medicament according to claim 1 or 2, in which (A) is formoterol fumarate.
4. A medicament according to claim 3, in which (A) is formoterol fumarate dihydrate.
5. A medicament according to any one of claims 1 to 4, which is in inhalable form.
6. A medicament according to claim 5, in which (A) and/or (B) are present in an atomizable composition.
7. A medicament according to claim 6, in which the inhalable form is an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant.
8. A medicament according to claim 6, in which the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium or a combination of a dispersion of (A) in said medium with a dispersion of (B) in said medium.
9. A medicament according to claim 5, in which (A) and/or (B) are present in a dry powder comprising finely divided (A) and/or (B) optionally together with a pharmaceutically acceptable carrier in finely divided form.
10. A medicament according to claim 9, in which the carrier is present and is a saccharide.

11. A medicament according to claim 9, in which the carrier is lactose.
12. A medicament according to claim 9, 10 or 11, in which (A) and/or (B) has an average particle diameter up to 10  $\mu\text{m}$ .
13. A medicament according to any one of the preceding claims, in which the weight ratio of (A) to (B) is from 2:1 to 1:2000.
14. A medicament according to claim 13, in which said ratio is from 1:10 to 1:25.
15. A medicament according to claim 2, which is a dry powder in a capsule, the capsule containing from 3 to 36  $\mu\text{g}$  of (A) as formoterol fumarate dihydrate, from 25  $\mu\text{g}$  to 800  $\mu\text{g}$  of (B) and a pharmaceutically acceptable carrier in an amount to bring the total weight of dry powder per capsule to between 5 mg and 50 mg.
16. A medicament according to claim 2, which is a dry powder comprising, by weight, from 3 to 36 parts of (A) as formoterol fumarate dihydrate, from 25 to 800 parts of (B) and 2164 to 24972 parts of a pharmaceutically acceptable carrier.
17. A pharmaceutical kit comprising (A) as defined in claim 1, 3 or 4 and (B) as defined in claim 1 in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts, together with one or more inhalation devices for administration of (A) and (B).
18. The use of (A) as defined in claim 1, 3 or 4 or (B) as defined in claim 1 in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.
19. The use of (A) as defined in claim 1, 3 or 4 and (B) as defined in claim 1 for the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.
20. A method of treating an inflammatory or obstructive airways disease which comprises administering to a subject in need of such treatment effective amounts of (A) as defined in claim 1, 3 or 4 and (B) as defined in claim 1.

## INTERNATIONAL SEARCH REPORT

Intern. nat Application No  
PCT/EP 00/01722

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K31/135 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 05805 A (ASTRA AB ;BRIGGNER LARS ERIK (SE); TROFAST EVA ANN CHRISTIN (SE)) 2 March 1995 (1995-03-02) page 7, line 33-37; examples 2,3,6 -----	1-20
P, Y	WO 99 18971 A (SCHERING CORP ;HARRIS DAVID (US); SEQUEIRA JOEL A (US); CHAUDRY IM) 22 April 1999 (1999-04-22) abstract; claim 1 -----	1-20
E	WO 00 15234 A (SCHERING CORP) 23 March 2000 (2000-03-23) page 4, line 25-30 -----	1-20 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

31 May 2000

Date of mailing of the International search report

08/06/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5810 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Gonzalez Ramon, N

## INTERNATIONAL SEARCH REPORT

Inte...inal Application No

PCT/EP 00/01722

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BARNES P.J.: "Efficacy of inhaled corticosteroids in asthma." JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1998) 102/4 I (531-538). , XP000911075 abstract page 535, column 1, paragraph 2 page 536, column 1, paragraph 3 ----	1-20
P,X	US 6 030 604 A (TROFAST JAN) 29 February 2000 (2000-02-29) claims 14-23	1-20
X	& WO 98 31352 A ----	
A	WO 98 34595 A (HERZOG KURT ;JAGO PHARMA AG (CH); KELLER MANFRED (DE)) 13 August 1998 (1998-08-13) claims 17,18; example 4 ----	1-20
X	WO 98 41193 A (SCHERING CORP) 24 September 1998 (1998-09-24) claims 4,50,51 ----	1-20
X	LIPWORTH B. ET AL: "Effects of treatment with formoterol on bronchoprotection against methacholine." AMERICAN JOURNAL OF MEDICINE, (1998) 104/5 (431-438). , XP000911068 abstract page 437, column 2, paragraph 3 ----	1-20
Y	O'CONNOR B.J.: "Combination therapy." PULMONARY PHARMACOLOGY AND THERAPEUTICS, (1998) 11/5-6 (397-399). , XP000911059 the whole document -----	1-20

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No  
PCT/EP 00/01722

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9505805	A 02-03-1995	AU 681186	B	21-08-1997
		AU 7626494	A	21-03-1995
		BR 9407320	A	16-04-1996
		CN 1133004	A, B	09-10-1996
		CN 1195523	A	14-10-1998
		CZ 9600544	A	15-05-1996
		EP 0717616	A	26-06-1996
		FI 960869	A	26-02-1996
		HU 74000	A	28-10-1996
		JP 2978247	B	15-11-1999
		JP 9501930	T	25-02-1997
		NO 960744	A	23-02-1996
		NZ 273090	A	24-06-1997
		PL 313142	A	10-06-1996
		SG 47760	A	17-04-1998
		SK 23496	A	05-02-1997
		US 5709884	A	20-01-1998
		US 5637620	A	10-06-1997
		US 5874063	A	23-02-1999
		ZA 9405675	A	29-04-1996
WO 9918971	A 22-04-1999	AU 9674398	A	03-05-1999
WO 0015234	A 23-03-2000	NONE		
US 6030604	A 29-02-2000	AU 5785998	A	07-08-1998
		CZ 9902557	A	13-10-1999
		NO 993539	A	20-09-1999
		PL 334527	A	28-02-2000
		WO 9831352	A	23-07-1998
		ZA 9800078	A	20-07-1998
		US 5980949	A	09-11-1999
		US 5983956	A	16-11-1999
WO 9834595	A 13-08-1998	AU 5649698	A	26-08-1998
		NO 993773	A	04-10-1999
		ZA 9800937	A	06-08-1998
WO 9841193	A 24-09-1998	AU 6537898	A	12-10-1998
		EP 0969816	A	12-01-2000
		NO 994519	A	19-11-1999
		ZA 9802254	A	17-09-1998